Complete Summary

GUIDELINE TITLE

Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine.

BIBLIOGRAPHIC SOURCE(S)

Marik PE, Pastores SM, Annane D, Meduri GU, Sprung CL, Arlt W, Keh D, Briegel J, Beishuizen A, Dimopoulou I, Tsagarakis S, Singer M, Chrousos GP, Zaloga G, Bokhari F, Vogeser M, American College of Critical Care Medicine. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. Crit Care Med 2008 Jun;36(6):1937-49. [127 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Critical illness-related corticosteroid insufficiency (adrenal insufficiency), including:

- Septic shock
- Acute respiratory distress syndrome (ARDS)

GUIDELINE CATEGORY

Diagnosis
Management

CLINICAL SPECIALTY

Critical Care
Emergency Medicine
Endocrinology
Family Practice
Internal Medicine
Pulmonary Medicine

INTENDED USERS

Advanced Practice Nurses
Health Care Providers
Hospitals
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To develop consensus statements for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients

TARGET POPULATION

Critically ill adult patients

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

Adrenal function testing:

- Delta total serum cortisol
- Random total serum cortisol

Note: The use of free cortisol assay cannot be recommended for use at this time. The adrenocorticotrophic hormone (ACTH) stimulation test should not be used to identify those patients with septic shock or acute respiratory disease (ARDS) who should receive glucocorticoids.

Treatment/Management

1. Hydrocortisone
2. Methylprednisolone
3. Fludrocortisone (optional)
4. Tapering of glucocorticoids
5. Reinstitution of treatment with recurrence of symptoms

Note: Dexamethasone is not recommended for the treatment of septic shock or ARDS.

MAJOR OUTCOMES CONSIDERED

- 28-day mortality
- Vasopressor dependency
- Adverse events of glucocorticoid (GC) therapy
- Duration of mechanical ventilation
- Intensive care unit length of stay
- Incidence of myopathy or neuropathy
- Immediate or prolonged suppression of hypothalamic-pituitary-adrenal (HPA) axis

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The task force members individually and collectively undertook a systematic search of published literature pertaining to the diagnosis and treatment of adrenal failure in critically ill adult patients using Medline, CINAHL, EMBASE, and the Cochrane library. In addition, the reference lists of relevant articles were reviewed for additional published works. Key words used in these searches included "pituitary–adrenal system, adrenal insufficiency, adrenal glands, pituitary–adrenal function tests, hydrocortisone, glucocorticoids (GC), adrenal cortex hormones, glucocorticoid receptor (GR), critical care, intensive care units, intensive care, ARDS, shock septic, sepsis, and sepsis syndrome."

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Delphi Method)
Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Modified Grades of Recommendation Assessment, Development, and Evaluation (GRADE) system for grading the strength of evidence

Grade of Recommendation/Description	Benefits vs. Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
1A: Strong recommendation, high quality evidence	Benefits clearly outweigh risk and burdens or vice versa	Randomized controlled trials (RCTs) without important limitations or overwhelming evidence from observational studies	Strong recommendation can apply to most patients in most circumstances without reservation
1B: Strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens or vice versa	RCTs with important limitations or exceptionally strong evidence from observational studies	Strong recommendation can apply to most patients in most circumstances without reservation
1C: Strong recommendation, low quality or very low quality evidence	Benefits clearly outweigh risk and burdens or vice versa	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
2A: Weak recommendation, high quality evidence	Benefits closely balanced with risk and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients or societal values
2B: Weak recommendation, moderate quality evidence	Benefits closely balanced with risk and burden	RCTs with important limitations or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients or societal values
2C: Weak recommendation, low quality or very low quality evidence	Uncertainty in the estimates of benefits, risks, and burdens; benefits	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

Grade of Recommendation/Description	Benefits vs. Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
	risk and burden may be closely balanced		

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

A meta-analysis of randomized controlled trials that compared the 28-day mortality and vasopressor dependency of patients with septic shock and the 28-day mortality of patients with acute respiratory distress syndrome (ARDS) who received either moderate-dose corticosteroid or placebo was performed. Four of the task force members reviewed the task force bibliography for relevant studies. Septic shock was defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference and ARDS by the American–European Consensus Conference. Vasopressor dependency was defined as the requirement for a vasopressor agent after 7 days of treatment with a glucocorticoid (GC). The reviewers independently abstracted data from all eligible studies. Data were abstracted on study design, study size, corticosteroid dosage, vasopressor dependency, and 28-day mortality. Study and data inclusion was by consensus. We used the random effects models using Review Manager 4.2 (Cochrane Collaboration, Oxford, UK) for all analyses and considered $p<.05$ (two-sided) as significant. Summary effects estimates are presented as odds ratio with 95% confidence intervals. The authors assessed heterogeneity between studies using the Cochran Q statistic with $p<.10$ indicating significant heterogeneity and the I^2 with suggested thresholds for low (25 to 49%), moderate (50 to 74%), and high (>75%) values (18 to 21).

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Delphi)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Experts were selected from the membership lists of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). Specific individuals were selected to represent geographic diversity and a broad range of expertise on the basis of their published research. In addition, endocrinologists with expertise in this area were invited to join the task force.

The authors used electronic mail to conduct the Delphi process. A list of questions for review was determined. Once a majority agreement was reached on each question, the strength of each recommendation was quantified using the Modified Grades of Recommendation Assessment, Development, and Evaluation (GRADE) system developed by the American College of Chest Physicians (see the "Rating Scheme for the Strength of the Evidence" field). In all, there were seven rounds until a majority agreement was achieved on all the questions. In addition, the group met in Paris, France, in September 2005 and again at the Society of Critical Care Medicine 35th Critical Care Congress in San Francisco, CA, in January 2006 to review the progress of the Delphi process. The initial draft of the manuscript was written by the Chair.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Refer to the "Rating Scheme for the Strength of the Evidence" field.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The draft manuscript was reviewed and iteratively edited by all members of the task force.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The strength of the recommendations (1A,1B, 1C, 2A, 2B, 2C) are defined at the end of the "Major Recommendations" field.

Critical Illness-Related Corticosteroid Insufficiency

Recommendation 1: Dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis in critical illness is best described by the term *critical illness–related corticosteroid insufficiency* (CIRCI).

Recommendation 2: The terms *absolute* or *relative* adrenal insufficiency are best avoided in the context of critical illness.

Diagnosis of Adrenal Insufficiency

Recommendation 3: At this time, adrenal insufficiency in critical illness is best diagnosed by a delta cortisol (after 250 micrograms cosyntropin) of <9 micrograms/dL or a random total cortisol of <10 micrograms/dL.

Strength of Recommendation: 2B

Recommendation 4: The use of free cortisol measurements cannot be recommended for routine use at this time. Although the free cortisol assay has advantages over the total serum cortisol, this test is not readily available. Furthermore, the normal range of the free cortisol in critically ill patients is currently unclear.

Strength of Recommendation: 2B

Recommendation 5: The adrenocorticotrophic hormone (ACTH) stimulation test should not be used to identify those patients with septic shock or acute respiratory distress syndrome (ARDS) who should receive glucocorticoids (GCs).

Strength of Recommendation: 2B

Who to Treat with Glucocorticoids

Recommendation 6: Hydrocortisone should be considered in the management strategy of patients with septic shock, particularly those patients who have responded poorly to fluid resuscitation and vasopressor agents.

Strength of Recommendations: 2B

Recommendation 7: Moderate-dose GC should be considered in the management strategy of patients with early severe ARDS (partial pressure of arterial oxygen/fraction of inspired oxygen [PaO_2/FIO_2] of <200) and before day 14 in patients with unresolving ARDS. The role of GC treatment in acute lung injury and less severe ARDS (PaO_2/FIO_2 of >200) is less clear.

Strength of Recommendations: 2B

How to Treat

Recommendation 8: In patients with septic shock, intravenous hydrocortisone should be given in a dose of 200 mg/day in four divided doses or as a bolus of 100 mg followed by a continuous infusion at 10 mg/hr (240 mg/day). The optimal initial dosing regimen in patients with early severe ARDS is 1 mg/kg/day methylprednisolone as a continuous infusion.

Strength of Recommendation: 1B

Recommendation 9: The optimal duration of GC treatment in patients with septic shock and early ARDS is unclear. However, based on published studies and pathophysiological data, patients with septic shock should be treated for ≥7 days before tapering, assuming that there is no recurrence of signs of sepsis or shock. Patients with early ARDS should be treated for ≥14 days before tapering.

Strength of Recommendation: 2B

Recommendation 10: GC treatment should be tapered slowly and not stopped abruptly.

Strength of Recommendation: 2B

Recommendation 11: Treatment with fludrocortisone (50 micrograms orally once daily) is considered optional.

Strength of Recommendation: 2B

Recommendation 12: Dexamethasone is not recommended for the treatment of septic shock or ARDS.

Strength of Recommendation: 1B

Definitions:

Grade of Recommendation/Description	Benefits vs. Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
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2A: Weak recommendation, high quality evidence	Benefits closely balanced	RCTs without important limitations or	Weak recommendation, best action may

Grade of Recommendation/Description	Benefits vs. Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
	with risk and burden	overwhelming evidence from observational studies	differ depending on circumstances or patients or societal values
2B: Weak recommendation, moderate quality evidence	Benefits closely balanced with risk and burden	RCTs with important limitations or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients or societal values
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CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations" field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate diagnosis and management of corticosteroid insufficiency in critically ill adult patients

POTENTIAL HARMS

Adverse effects of steroids, including myopathy and superinfection

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Timeliness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2008 Jun

GUIDELINE DEVELOPER(S)

Society of Critical Care Medicine - Professional Association

SOURCE(S) OF FUNDING

Society of Critical Care Medicine (SCCM)

GUIDELINE COMMITTEE

Society of Critical Care Medicine Task Force

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Authors: Paul E. Marik, MD, FCCM; Stephen M. Pastores, MD, FCCM; Djillali Annane, MD; G. Umberto Meduri, MD; Charles L. Sprung, MD, FCCM; Wiebke Arlt, MD; Didier Keh, MD; Josef Briegel, MD; Albertus Beishuizen, MD; Ioanna Dimopoulou, MD; Stylianos Tsagarakis, MD, PhD; Mervyn Singer, MD; George P. Chrousos, MD; Gary Zaloga, MD, FCCM; Faran Bokhari, MD, FACS; Michael Vogeser, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Dr. Marik has received lecture fees from Eli Lilly and Merck.

Dr. Keh has received grant support from the German Research Foundation and German Ministry of Education and Research (HYPRESS: Hydrocortisone for Prevention of Septic Shock).

Dr. Sprung has been a member of a data monitoring and safety committee for Artisan Pharma, Novartis Corporation, and Hutchinson Technology Incorporated. He has served as a consultant for AstraZeneca, Eisai Corporation, Eli Lilly, and GlaxoSmithKline. He has received grant support from the European Commission, Takeda, and Eisai Corporation. He has received lecture fees from Eli Lilly.

Drs. Sprung, Annane, Keh, Singer, and Briegel were investigators in the CORTICUS study, which was supported by the European Commission, the European Society of Intensive Care Medicine, the European Critical Care Research Network, the International Sepsis Forum, and the Gorham Foundation.

Dr. Annane has received grant support from the French Ministry of Health for the prognostic value of a adrenocorticotrophic hormone test in septic shock; the French multicenter, randomized, controlled trial on hydrocortisone plus fludrocortisone in septic shock; the ongoing French multicenter 2X2 factorial study that compares strict glucose control vs. conventional treatment for steroid-treated septic shock and hydrocortisone alone vs. hydrocortisone and fludrocortisone; and a French multicenter 2X2 factorial trial that compares hydrocortisone plus fludrocortisone, activated protein C, the combination of the two drugs, and placebos for the treatment of septic shock.

Dr. Pastores has received grant support from Eisai Medical Research (phase 3 trial of E5564 in severe sepsis), and Artisan Pharma (phase 2 sepsis with disseminated intravascular coagulation trial).

The remaining authors have not disclosed any conflicts of interest with respect to this article.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Society of Critical Care Medicine (SCCM) Web site.

Print copies: Available from the Society of Critical Care Medicine, 701 Lee Street, Suite 200, Des Plaines, IL 60016; Phone: (847) 827-6869; Fax: (847) 827-6886; on-line through the SCCM Bookstore.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI Institute on September 4, 2008. The information was verified by the guideline developer on October 20, 2008.

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